Remarks

Claims 4-6, 18, 24, 25, 30, 81, 90, 97, 168, 177, 182, 184, 188, 191, 195, 197, 210, 261 and 320 are cancelled. Applicant reserves the right to pursue the subject matter of the originally filed claims in continuing applications.

Claims 1, 251 and 252 are amended to recite chemical structures. Support for these amendments can be found in the specification at least on page 3 lines 10-29 and page 4 lines 9-17. Claims 1, 3, 8-17, 139, 142, 144 and 166 are further amended to recite anti-CD20 antibody or a fragment thereof. Support for these amendments can be found in the specification at least on page 7 lines 7-9 and in claim 6 as originally filed. Claim 1 is further amended. Support for this amendment can be found in the specification at least on page 2 lines 13-16 and 25-27 and page 50 lines 13-17.

Claims 340-347 are added. Support for claims 340 and 345 can be found in the specification at least on page 5 line 28 and page 59 lines 23-32. Support for claim 341 can be found in the specification at least on page 5 line 6. Support for claims 342 and 346 can be found in the specification at least on page 7 lines 26-28. Support for claims 343, 344 and 347 can be found in the specification at least on page 11 lines 8-13.

Claims 1-3, 7-17, 139, 142, 144, 166, 251-260, 338 and 340-347 are pending.

No new matter has been added.

Rejection under 35 U.S.C. §112

Claims 1-17, 25, 139, 142, 144, 166, 210, 251-260 and 338 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. In particular, the Examiner considers the rejected claims vague and indefinite in the recitation of Formulae I-III, which the Examiner regards as "laboratory designations". Applicant respectfully traverses since these claims are not mere laboratory designations and rather are explicitly defined in the specification at least on page 3 line 10 through to page 4 lines 17. Notwithstanding this and in the interest of expediting prosecution, Applicant has amended claims 1, 251 and 252 to include these chemical structures. Claims 25 and 210 are now cancelled.

Claim 257 is amended to change dependency from claim 1 to claim 255, which recites IL-1.

In view of the foregoing, reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §102

Claims 1-3, 8, 11, 14, 15, 25, 251, 253-254, 258, 260 and 338 are rejected under 35 U.S.C. §102(b) as being anticipated by Wallner et al. (WO 00/71135).

Claim 1 has been amended to recite that treatment of a subject having cancer with an anti-CD20 antibody is enhanced by using the antibody in conjunction with an agent of Formula I. Support for this amendment can be found in the specification at least on page 2 lines 13-16 and 25-27 and page 50 lines 13-17 and in Fig. 3. The Figure demonstrates, in a murine (NOD/SCID) mouse model of Burkitt's Non-Hodgkin's lymphoma, that when the anti-CD20 antibody rituximab is used together with the Formula I agent Val-boroPro (i.e., PT-100), the effect of the antibody on tumor volume is enhanced. This effect has also been demonstrated in clinical trials in subjects that were refractory to a prior regimen of rituximab. These subjects responded to the antibody when it was administered in conjunction with the Formula I agent Val-boroPro. Applicant includes herewith a copy of a poster describing these clinical data which were presented at the American Society of Hematology Annual Meeting in December 2005.

Wallner et al. does not disclose the combination of an anti-CD20 antibody with an agent of Formula I. Wallner et al. also does not disclose that the agent of Formula I, when used in conjunction with the anti-CD20 antibody, actually enhances the effect of the antibody in a subject having cancer. The reference therefore does not anticipate the claims as amended.

Reconsideration and withdrawal of the rejection is respectfully requested.

Rejections under 35 U.S.C. §103

Wallner et al. (WO 00/71135)

Claims 12-13, 16-17, 139, 210 and 259 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wallner et al. (WO 00/71135).

Claim 210 has been cancelled. Claim 1, from which all other rejected claims depend, has been amended to recite a method for enhancing treatment with an anti-CD20 antibody by using the antibody in conjunction with an agent of Formula I. This combination of agents and its enhanced anti-cancer effect are not suggested in Wallner et al. It would not have been obvious to one of ordinary skill in the art based on the disclosure of Wallner et al. that the efficacy of an anti-CD20 antibody could be enhanced by administering it with an agent of Formula I. The rejected claims are therefore not rendered obvious by the reference.

Reconsideration and withdrawal of the rejection is respectfully requested.

Wallner et al. (WO 00/71135) in view of Wallner et al. (WO99/56753)

Claims 252 and 255 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wallner et al. (WO/71135) in further view of Wallner et al. (WO 99/56753).

Claims 252 and 255 depend from claim 1. Claim 1 has been amended to recite a method for enhancing treatment with an anti-CD20 antibody by using the antibody in conjunction with an agent of Formula I. The combination of the references, even if proper, does not result in the claimed invention at least because neither reference discloses or suggests an anti-CD20 antibody, its use in conjunction with an agent of Formula I, and the enhanced efficacy resulting therefrom.

Reconsideration and withdrawal of the rejection is respectfully requested.

Wallner et al. (WO 00/71135) in view of Hudziak et al. (US 5,725,856)

Claims 4, 9, 10, 142 and 144 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wallner et al. (WO 00/71135) in further view of Hudziak et al. (U.S. Patent No. 5,725,856).

Claim 1, from which all the rejected claims depend, has been amended as described above. In particular, claim 1 now recites an anti-CD20 antibody and the increased efficacy of such an antibody when used in conjunction with an agent of Formula I.

Wallner et al. does not disclose an anti-CD20 antibody nor the ability to enhance the efficacy of such an antibody by using it in conjunction with an agent of Formula I. Hudziak et al. does not provide the deficiencies of Wallner et al. Hudziak et al. discloses anti-HER2 antibodies. Hudziak et al. does not teach anti-CD20 antibodies nor does it teach the increased therapeutic efficacy that can be achieved when these antibodies are used together with an agent

of Formula I. Thus, even if the references could be combined, the combination would not yield the claimed invention.

Reconsideration and withdrawal of the rejection is respectfully requested.

Wallner et al. (WO 00/71135) in view of Borisy et al. (US 2002/0165261)

Claims 4-7 and 166 are rejected under 35 U.S.C. §103(a) as being unpatentable over Wallner et al. (WO 00/71135), in further view of Borisy et al. (U.S. Patent Application No. 2002/0165261).

Wallner et al. has been discussed above. The Examiner cites Borisy et al. for the teaching that rituximab and other agents are chemotherapeutic drugs currently in use or in clinical trials. (See Background of the Invention.) Apart from this, however, the focus of Borisy et al. is the use of particular antihelmintic drugs with a particular antiprotozoal drug for the treatment of cancer.

The references cannot be combined at least because there is no reasonable expectation of success, as discussed in greater detail below. Moreover, even if the references could be combined, the combination does not result in the claims as amended which recite that treatment with an anti-CD20 antibody is *enhanced* by an agent of Formula I. The instant specification documents this enhanced response in a mouse model of Burkitt's Non-Hodgkin's lymphoma in Fig. 3 and Example 4. In this model, when the anti-CD20 antibody rituximab was administered in conjunction with the Formula I agent Val-boroPro (i.e., PT-100), tumor growth was inhibited to a significantly greater extent than occurred with the antibody alone. Submitted herewith is a Declaration under 37 CFR § 132 of Dr. Barry Jones describing these results.

Similar results have been observed during Phase II clinical trials using rituximab and Val-boroPro. These latter results were presented at the American Society of Hematology Annual Meeting in December 2005. These data show that anti-cancer responses can be achieved using rituximab and Val-boroPro in patients who failed a prior rituximab regimen. These trials were conducted in accordance with methods described in the instant patent application. The results demonstrate that the therapeutic effect of the anti-CD20 antibody can be enhanced by using the antibody in conjunction with a Formula I agent, and thus they further support the invention as

described in this instant application and as claimed. Submitted herewith is a Declaration under 37 CFR § 132 of Dr. Margaret J. Uprichard describing these results.

It was unpredictable prior to the invention that enhanced efficacy of an antibody (such as rituximab) could be achieved by combining it with an agent of Formula I (such as Val-boroPro). One reason for the lack of predictability is the difference in the mechanisms of action of these agents as understood prior to the invention. The anti-cancer effect of antibodies such as anti-CD20 antibodies is mediated via an immunological mechanism of action. It was not appreciated, prior to the invention, that Formula I agents such as Val-boroPro could also mediate effects via an immunological mechanism. Therefore the ability of a presumably non-immunologically acting anti-cancer agent to enhance the efficacy of an immunologically acting anti-cancer antibody could not have been predicted and thus was unexpected.

For at least these reasons there was no reasonable expectation of success relating to the combination of the references. However, even if a prima facie case of obviousness existed (and Applicant maintains it does not), the claimed invention provides unexpected results that are to be taken into account by the Examiner in his determination of obviousness. In re May 574 F.2d 1082, 197 USPQ 601 (CCPA 1978). The evidence provided in the specification and in the Declarations submitted herewith is commensurate with and supportive of the unexpected nature of the claimed invention.

Accordingly, the claimed invention was not obvious because one of ordinary skill would not have expected the effect of an anti-CD20 antibody to be enhanced through the use of a Formula I agent.

Reconsideration and withdrawal of the rejection is respectfully requested.

Double Patenting Rejection

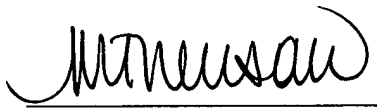
Claims 1-3 and 210 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 112 and 362 of co-pending Application No. 10/616,694. Without conceding the Examiner's position, Applicant defers substantive rebuttal until the cited claims are allowed.

Conclusion

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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Docket No.: I0248.70024US00
Date: April 21, 2006
x04/21/06x